Genomic and Clinical Correlates of Belzutifan Treatment in Renal Cell Carcinoma (RCC): A Retrospective Analysis of 150 RCC Patients

Harshitha Dudipala,[1] Yu-Wei Chen,[1] Shayan S. Nazari,[2] Andrew Elliot,[2] Ninad Kulkarni,[2] Rashad Nawfal,[3] Liliana Asclone,[3] Marc Machaalani,[3] David McDermott,[3] Sabina Signoretti,[3] Pedro Barata,[4] Brent Rose,[1] Aditya Bagrodia,[1] Neeraj Agarwal,[5] Sumanta Pal,[6] Toni K. Choueiri,[3] Rana R. McKay,[1]

1) Department of Medicine, Moores Cancer Center, University of California San Diego, La Jolla, CA. 2) Caris Life Sciences, Phoenix, AZ.
3) Dana-Farber Cancer Institute, Boston, MA. 4) University Hospitals Seidman Cancer Center, Cleveland, OH. 5) University of Utah, Huntsman Cancer Institute, Salt Lake City, UT. 6) City of Hope, Duarte, CA.

Abstract #4541

BACKGROUND

- In approximately 90% of clear cell RCC, the von Hippel-Lindau (VHL) tumor suppressor gene is inactivated or lost.
- This can lead to buildup of hypoxia-inducible factor-2α (HIF-2α) → leading to uncontrolled angiogenesis and tumor growth.
- Belzutifan is a HIF-2α inhibitor approved for RCC that targets a central driver in RCC pathogenesis.
- However, predictive biomarkers of response remain poorly defined.

METHODS

- 150 belzutifan-treated RCC tumors were included in the analysis, of which 29% were primary kidney tumors and the remainder were from metastatic sites.
- Clear cell RCC and RCC-NOS with *VHL* mutations were included.
- Comprehensive DNA (592-gene panel or whole exome) and RNA (whole transcriptome) sequencing were performed by Caris Life Sciences on RCC samples.
- Belzutifan median time on treatment (ToT) within our study population was 85 days (95% CI: 71–114), which was derived from insurance claims
- Classification of responders (n=57) vs. non-responders (n=93) was based on ToT, with responders defined as greater than median ToT, and non-responders defined as less than median ToT.

RESULTS

Figure 1: Gene expression among responders vs non-responders in Belzutifan treated RCC patients

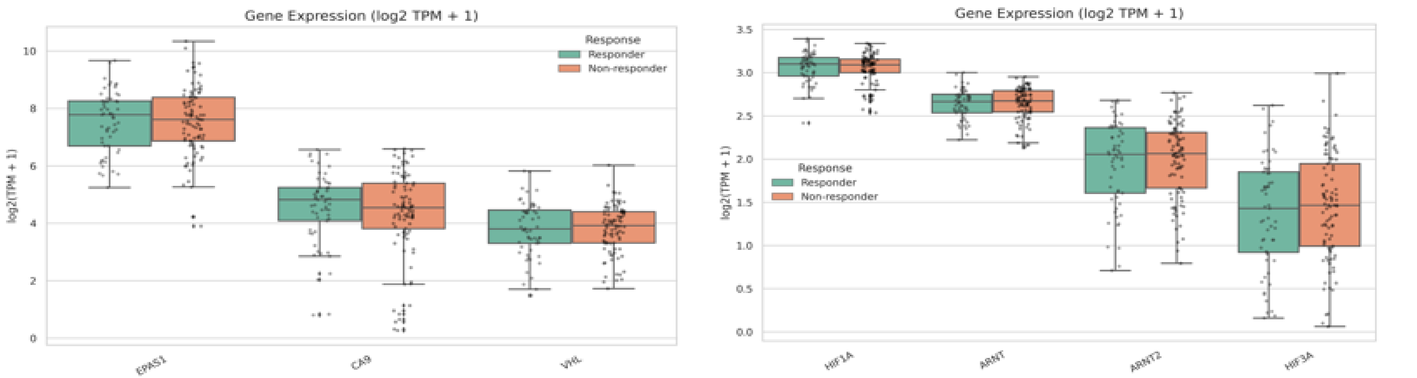
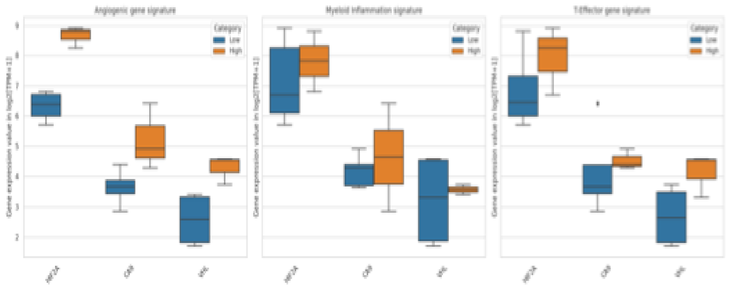


Figure 2: HIF gene expression and angiogenic, myeloid inflammation and T-effector cell signature scores

A. Responders



B. Non-responders

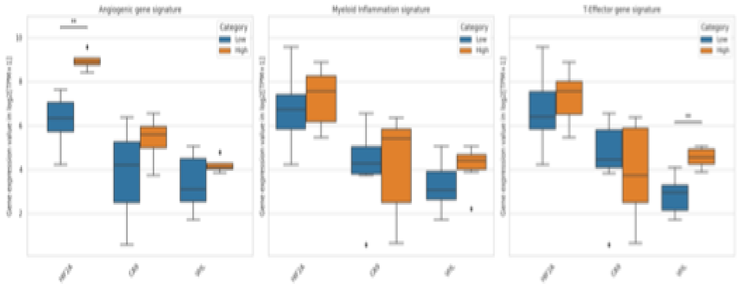


Figure 3: Mutation frequencies in Belzutifan treated RCC patients

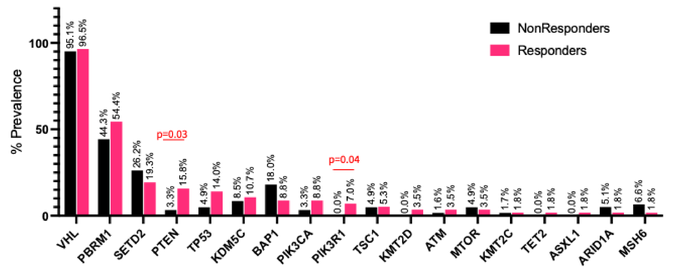
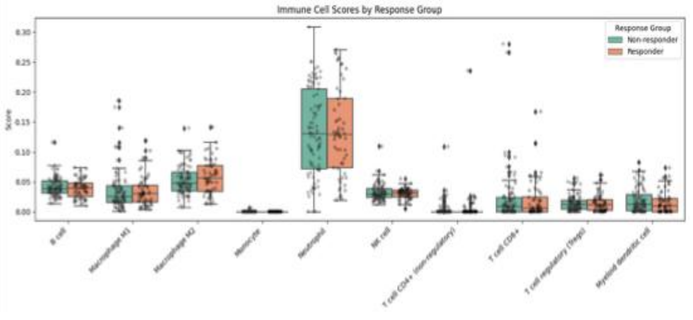


Figure 4: Immune cell microenvironment by response



- Baseline characteristics were similar, except responders were younger (median age 57 vs 64 years, p=0.007).
- Transcriptomic analysis showed similar HIF-2α (median 7.78 vs 7.61) and *CA9* (4.82 vs 4.54) expression between responders and non-responders without statistical significance (Figure 1).
- Higher HIF-2a gene expression is associated with higher angiogenic gene signatures in non-responders (p= 0.001), and higher *VHL* gene expression is associated with higher T-effector gene signatures (= 0.001) (Figure 2).
- Responders showed significant enrichment of *PTEN* (15.8% vs. 3.3%, p=0.03) and *PIK3R1* alterations (7.0% vs. 0.0%, p=0.04), and numerically higher frequencies of *PBRM1* and *PIK3CA* mutations (Figure 3).
- Alterations in DNA damage response gene *ATM* were more common among responders, while non-responders showed higher frequencies of *BAP1* (18% vs 8.8%), *SETD2* (26.2% vs 19.3) and *ARID1A* (5.1% vs1.8%) alterations (Figure 3).
- No significant differences were seen within immune cell microenvironment (Figure 4).

CONCLUSIONS

- HIF2-α RNA expression alone does not predict belzutifan response in RCC.
- Responders demonstrated alterations in *PBRM1*, PI3K/AKT/mTOR, and DNA damage response genes, while non-responders showed numerically higher frequencies of chromatin remodeling mutations including *BAP1* and *SETD2*.
- Study limitation included small sample size and short follow-up. Larger datasets are required to validate these findings.

Corresponding Authors:
Harshitha Dudipala, MD: harshitha.dudipala@health.ucsd.edu
Yu-Wei Chen, MD: yuc209@health.ucsd.edu
Rana R. McKay, MD: rmckay@health.ucsd.edu
@HersheyDudipala